IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	STEINMAN *et al.*	Docket No.:	ARG010RC
Serial No.:	09/073,596	Filing Date:	May 6, 1998
Examiner:	Gerald R. Ewoldt	Art Unit:	1644
Customer No.:	43852	Confirmation No.	9977

Title: METHOD FOR IN VITRO PROLIFERATION OF DENDRITIC CELL PRECURSORS AND THEIR USE TO PRODUCE IMMUNOGENS

* * *

RESPONSE TO NOTIFICATION OF NON-COMPLIANT BRIEF FOR APPEAL UNDER 37 CFR § 41.37

September 9, 2010

Mail Stop Appeal Brief—Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants previously timely submitted a Brief to appeal the Examiner's final rejections as set forth in the Office Action mailed February 23, 2010 (the "final Office Action"). A Notification of Non-Compliant Appeal Brief was mailed August 9, 2010, stating that the brief was defective because the Appeal Brief's Summary of Claimed Subject Matter improperly mapped independent claims 101, 120, and 145 as a group and stating that only the corrected section needed to be filed to correct the error. In addition, the previously submitted Appeal Brief had omitted page numbers on each page. Accordingly, herewith is a substitute Appeal Brief with page numbers on each page and a corrected Summary of Claimed Subject Matter section that corrects the defect by mapping each of independent claims 101, 120, and 145 separately. Because the Notification of Non-Compliant Appeal Brief indicated that only the corrected portion need be resubmitted, this paper includes only the Appeal Brief, Claims Appendix, and first page of the Evidence Appendix.

The Notification of Non-Compliant Appeal Brief was mailed August 9, 2010, and set a response period of one month or thirty days, whichever was longer; accordingly, this paper is timely filed.

Reversal of the Examiner's rejections of claims 99, 101, 103-113, 116, 120 and 142-145 by the Board of Patent Appeals and Interferences (the "Board") is respectfully requested.

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I. REAL PARTY IN INTEREST

Argos Therapeutics, Inc., and The Rockefeller University are the assignees of rights in the subject application, as well as the invention disclosed and claimed therein, by virtue of the assignments recorded in the PTO on: September 21, 2001, starting at reel 012199 and frame 0923 (assignment from inventor Gerold Schuler to Merix Bioscience, Inc.; also recorded on September 10, 2003 at reel 013961 and frame 0748); April 30, 2008, starting at reel 020876 and frame 0811 (assignment from inventors Ralph Steinman and Kayo Inaba to The Rockefeller University); and documentation of change of name of Merix Bioscience, Inc. to Argos Therapeutics, Inc. recorded in the PTO on February 15, 2007 at reel 018942 and frame 0265.

Geron Corp. holds a license to certain rights in the application. Argos Therapeutics, Inc. has power of attorney for this application as recorded on November 18, 2004.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representative do not know of any prior or pending appeal, interference, or judicial proceeding which is related, directly affects, or is affected by the Board's decision in this appeal. Notices of Appeal were filed for this application on July 9, 2001 and August 14, 2003, but the appeal process was not continued; instead, prosecution was re-entered.

III. STATUS OF CLAIMS

Claims 99, 101, 103-113, 116, 120 and 142-145 stand rejected. They are at issue in this appeal and listed in the Claims Appendix.

Claims 1-98, 100, 102, 103, 114, 115, 117-119, and 121-141 were canceled without prejudice or disclaimer.

IV. STATUS OF AMENDMENTS

No amendment was filed subsequent to final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention involved in this appeal is directed to an *in vitro* composition comprising mature dendritic cells expressing modified antigen and derived from an *in vitro* culture of an enriched and expanded population of proliferating dendritic cell precursors by a specified method that comprises, *inter alia*, a step of culturing the tissue source on a substrate in a culture medium comprising GM-CSF; see, *e.g.,* page 25, lines 19-23, which explain that:

> "GM-CSF has surprisingly been found to promote the proliferation in vitro of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors."

Support for independent claim 101 is found, *inter alia*, in the first paragraph of the Detailed Description (page 19, lines 25-31), which explains that:

> "This invention relates to a method of producing cultures of proliferating dendritic cell precursors which mature *in vitro* to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method

> of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease."

The specification explains in the "Summary of Invention" (page 9, line 35 through page 10, line 3) that:

> "Another embodiment of the invention [is] antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells."

The specification also describes (*e.g.*, on page 40, lines 25-28) the benefits of the invention:

> "The present invention provides for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been activated with antigens."

As exemplified by these passages, the terminology used in the specification to describe the embodiments of the invention (such as these dendritic cells that have been activated with antigens) is not identical throughout the specification but rather explains the various embodiments in terms that will be understood by one of skill in the art. However, the specification when read as a whole and the passages above when read in the context of the specification provides ample support for the subject matter of claim 101 and the other claims.

Support for the method steps of claim 101 can be found, *inter alia*, in the specification on page 8, line 30 through page 9, line 10 and on page 9, line 35 through page 10, line 4, which are as follows (respectively):

> "This invention also provides a method of producing *in vitro* mature dendritic cells from proliferating cell cultures. The method comprises (a) providing a tissue source comprising dendritic cell precursor cells; (b) treating the tissue source from (a) to increase the proportion of dendritic cell precursors in order to obtain a population of cells suitable for culture in vitro; (c) culturing the tissue source on a substrate in a culture medium comprising GM-CSF, or a biologically active derivative of GM-CSF, to obtain non-adherent cells and cell clusters; (d) subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors; (e) serially subculturing the cell aggregates one or more times to enrich the proportion of dendritic cell precursors; and (f) continuing to culture the dendritic cell precursors for a period of time sufficient to allow them to mature into mature dendritic cells."

> "Another embodiment of the invention are antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells."

Additional support for the last method step of claim 101 can be found, for example, on page 34, line 33 through page 35, line 9 and page 36, line 31 through page 37, line 4, which are as follows:

> "The antigen-activated dendritic cells of the invention are produced by exposing antigen, in vitro, to the dendritic cells prepared according to the method of the invention. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells. The amount and time necessary to achieve binding of the antigen to the dendritic cells may be determined by immunoassay or binding assay. Other methods known to those of skill in the art may be used to detect the presence of antigen on the dendritic cells following their exposure to antigen."

> "Cells should be exposed to antigen for sufficient time to allow antigens to be internalized and presented on the cell surface. The time necessary for the cells to internalize and present the processed antigen may be determined using pulse-chase protocols in which exposure to antigen is followed by a wash-out period. Once the minimum time necessary for cells to express processed antigen on their surface is determined, a pulse-chase protocol may be used to prepare cells and antigens for eliciting immunogenic responses."

Discussion of the modification (processing) of the antigen by the dendritic cells is also discussed on page 41, line 29 through page 42, line 24.

Support for independent claim 120 is found, *inter alia*, in the first paragraph of the Detailed Description (page 19, lines 25-31), which explains that:

> "This invention relates to a method of producing cultures of proliferating dendritic cell precursors which mature *in vitro* to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease."

Page 25, lines 19-23, explain that:

> "GM-CSF has surprisingly been found to promote the proliferation in vitro of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors."

The specification explains in the "Summary of Invention" (page 9, line 35 through page 10, line 3) that:

> "Another embodiment of the invention [is] antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells."

The specification also describes (*e.g.*, on page 40, lines 25-28) the benefits of the invention:

> "The present invention provides for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been activated with antigens".

As discussed above for claim 101, while the terminology used in the specification to describe the embodiments of the invention is not identical throughout the specification, nevertheless the specification when read as a whole and the passages above when read in the context of the specification provides ample support for the subject matter of claim 120 and the other claims. The different terminology employed in the independent claims resulted largely from Appellants' repeated efforts to present claim language that would satisfy the Examiner's application of the written description requirement.

Support for the method steps set forth in claim 120 can be found, *inter alia*, in the passage reproduced above regarding the use of GM-CSF (on page 25, lines 19-23) and also on page 18, lines 26-29: "[t]o further expand the population of dendritic cells, cell aggregates may be serially subcultured multiple times at intervals which provide for the continued proliferation of dendritic cell precursors." Support for the last clause of claim 120 is also found on page 9, line 35 through page 10, line 4, which state that:

> "Another embodiment of the invention are antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells."

Additional support for the step of exposing the cells to antigen can be found, for example, on page 34, line 34 through page 35, line 9 and page 36, line 31 through page 37, line 4.

Support for independent claim 145 is found, *inter alia*, in the first paragraph of the Detailed Description (page 19, lines 25-31), which explains that:

> "This invention relates to a method of producing cultures of proliferating dendritic cell precursors which mature *in vitro* to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease."

Page 25, lines 19-23, explain that:

> "GM-CSF has surprisingly been found to promote the proliferation in vitro of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors."

The specification explains in the "Summary of Invention" (page 9, line 35 through page 10, line 3) that:

> "Another embodiment of the invention [is] antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells."

As discussed above for claim 101 and 120, while the terminology used in the specification to describe the embodiments of the invention is not identical throughout the specification, nevertheless the specification when read as a whole and the passages above when read in the context of the specification provides ample support for the subject matter of the claims. The different terminology employed in the independent claims resulted largely from Appellants' repeated efforts to present claim language that would satisfy the Examiner's application of the written description requirement; accordingly, the terminology in claim 145 differs from that of claim 101.

Support for the method steps set forth in claim 145 can be found, *inter alia*, in the specification on page 8, line 30 through page 9, line 10 and on page 9, line 35 through page 10, line 4, which are as follows, respectively:

> "This invention also provides a method of producing *in vitro* mature dendritic cells from proliferating cell cultures. The method comprises (a) providing a tissue source comprising dendritic cell precursor cells; (b) treating the tissue source from (a) to increase the proportion of dendritic cell precursors in order to obtain a population of cells suitable for culture in vitro; (c) culturing the tissue source on a substrate in a culture medium comprising GM-CSF, or a biologically active derivative of GM-CSF, to obtain non-adherent cells and cell clusters; (d) subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors; (e) serially subculturing the cell aggregates one or more times to enrich the proportion of dendritic cell precursors; and (f) continuing to culture the dendritic cell precursors for a period of time sufficient to allow them to mature into mature dendritic cells."

> "Another embodiment of the invention are antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells."

Additional support for step (g) of claim 145 can be found, for example, on page 34, line 33 through page 35, line 9 and page 36, line 31 through page 37, line 4, which are as follows:

> "The antigen-activated dendritic cells of the invention are produced by exposing antigen, <u>in vitro</u>, to the dendritic cells prepared according to the method of the invention. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells. The amount and time necessary to achieve binding of the antigen to the dendritic cells may be determined by immunoassay or binding assay. Other methods known to those of skill in the art may be used to detect the presence of antigen on the dendritic cells following their exposure to antigen."

> "Cells should be exposed to antigen for sufficient time to allow antigens to be internalized and presented on the cell surface. The time necessary for the cells to internalize and present the processed antigen may be determined using pulse-chase protocols in which exposure to antigen is followed by a wash-out period. Once the minimum time necessary for cells to express processed antigen on their surface is determined, a pulse-chase protocol may be used to prepare cells and antigens for eliciting immunogenic responses."

Discussion of the modification (processing) of the antigen by the dendritic cells is also discussed on page 41, line 29 through page 42, line 24. The term "pulsing" is understood in the art to describe exposing a cell to an antigen, for example, as it is used in the specification on page 8, line 1, page 43, line 1, and in the Abstract.

Dependent claim 104 (specifying that the tissue source is blood) is supported by page 23, lines 17-19; dependent claim 107 (specifying that the concentration of GM-CSF in the culture medium is about 30-100 U/ml) by page 25, lines 29-13; dependent claim 112 (specifying that the tissue source is treated to remove blood cells) by page 20, lines 34-36 and page 21, lines 10-12; dependent claim 105 (specifying that the tissue source is bone marrow) by page 21, lines 19-21; dependent claim 108 (specifying that the concentration of GM-CSF in the culture medium is about 500-1000 U/ml) by page 26, lines 1-6; dependent claim 113 (specifying that the tissue source is treated to remove B cells and granulocytes) by page 21, line 19 through page 22, line 3; dependent claim 106 (specifying that GM-CSF is present in the culture medium at a concentration of about 1-1000 U/ml) by page 25, lines 27-29; dependent claim 109 (specifying that the cell aggregates are blood-derived and are subcultured from about one to five times) by page 29, lines 21-35; dependent claim 110 (specifying that the cell aggregates are subcultured one to five times) by page 29, lines 34-36; dependent claim 111 (specifying that the culture medium is selected from a specified group and is supplemented with serum) by page 25, lines 2-6; dependent claim 116 (drawn to a pharmaceutical composition comprising the composition of claim 101) by page 42, lines 10-23; dependent claim 99 (specifying that the dendritic cells express an amount of the modified antigen to provide between about 1 to 100 micrograms of the modified antigen) by page 42, lines 23-25; dependent claim 142 (specifying that the dendritic cell precursors are human) by, *e.g.*, page 12, lines 18-22 and page 28, lines 3-6; dependent claim 143 (specifying that the dendritic cell precursors are obtained from blood) by page 23, lines 17-19; and dependent claim 144 (specifying that the dendritic cells are obtained from bone marrow) by page 21, lines 19-21. Additional support for these claims can generally also be found in the specification.

Therefore, the invention as presently claimed is clearly supported by the disclosure as originally filed.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Was it proper to deny the benefit of the priority claim to the application? (no statutory basis for this decision was specified in the Office Action, although it seems like a rejection under 35 U.S.C. § 112, first paragraph)

B. Under 35 U.S.C. § 102(a), was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly anticipated?

C. Under 35 U.S.C. § 103(a), was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly obvious?

D. Under 35 U.S.C. § 112, first paragraph, was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly containing new matter?

E. Under 35 U.S.C. § 112, second paragraph, was it proper to reject claim 120 as allegedly indefinite?

VII. ARGUMENTS

The claims do not all stand or fall together because the Board may reverse in part the denial of the benefit of the priority claim and the rejection under 35 U.S.C. §112, first paragraph, and may come to different conclusions for independent claims 101, 120, and 145. Claims 99, 104-113, 116, and 142-144 depend from or incorporate the limitations of independent claim 101 and stand or fall together with independent claim 101. The rejections of independent claim 120 and independent claim 145 may be reversed or affirmed separately from each other and separately from claim 101 and its dependent claims.

Claim 120 is the only claim rejected under 35 U.S.C. §112, second paragraph, and so this rejection may be affirmed by the Board even if the other rejections are reversed.

Priority Claim

The disclosure as originally filed need not provide "*in haec verba* support for the claimed subject matter at issue," rather, the disclosure should convey to one skilled in the art that the inventor had possession of the invention at the time of filing. *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). The Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have

recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

A. The final Office Action states that the priority claim for the present application is denied because, allegedly, "the applications do not disclose the invention of the instant claims." No claim numbers or statutory basis for the denial of the priority claim are specified, so these remain unclear. However, the statements in the Office Action regarding the denial of the priority claim appear to be based on the written description requirement of 35 U.S.C. § 112, first paragraph, and appear to apply to all of the claims, they will be addressed as if this had been explicitly stated in the Office Action.

Support in the present specification for each claim is discussed in the Summary of Claimed Subject Matter (section V) above. As can be seen, for example, from these passages, slightly different terminology is used in some parts of the specification to describe these dendritic cells that have been activated with antigens. Nevertheless, the specification when read as a whole fully supports all of the present claims. Corresponding support is found in the priority application (the "'612 application), as detailed for all of the claims in the chart provided in Appendix A; a copy of the '612 application is provided as Appendix B. The language of the pending claims has been drafted to conform as closely as possible to the exact language used in the present specification and to the language of the '612 priority application, both of which fully support the present claims. The support for the claims in the '612 application cited in Appendix A is also found in every application in the priority chain, including the instant application (No. 09/073,596).

The claimed invention is described throughout the present application and relates to compositions and methods for providing them which involve culturing dendritic cell precursors *in vitro* in the presence of GM-CSF, which ultimately produces mature dendritic cells. The invention also provides methods and compositions that further involve exposing the cells to antigen, which produces antigen-activated mature dendritic cells that express modified antigens. The mature dendritic cells and the antigen-activated mature dendritic cells as well as the methods of producing them are all embodiments of the invention. The specification discusses these various aspects of the invention throughout, particularly, for example, in the Summary of the Invention (page 8, line 13 through page 10, line 28); further embodiments and aspects of the invention are described in the remainder of the same Summary of the Invention section.

Antigen-activated dendritic cells (also referred to, *inter alia*, as dendritic cells expressing modified antigen) are dendritic cells that are prepared according to the methods of the invention and are further (*i.e.*, *additionally*) treated by exposure to antigen. That is, "[a]ntigen-activated dendritic cells [can be] prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells" (specification at page 9, line 35 through page 10, line 3). In other words, the methods of the invention are equally applicable to "antigen-activated dendritic cells," but additional steps beyond the standard methods are necessary to produce these activated cells.

A reading of the specification as a whole reveals that the specification describes various embodiments of the invention and fully supports the present claims. Corresponding support is also found in the priority application. Accordingly, the benefit of the priority claim should be accorded to the present application and the Board should reverse the denial of the priority claim.

35 U.S.C. §102—Anticipation

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

B. The final Office Action alleges that claims 99, 101, 104-113, 116, 120, and 142-145 are anticipated under 35 U.S.C. § 102(a) over Pancholi *et al.* (1992) *Immunology* 76: 217-224 ("Pancholi"). As noted in the Office Action, the Pancholi reference is not available as prior art if the priority claim for the present application is accorded full weight because the Pancholi reference was published in June 1992, after the filing date of the '612 priority application, which was April 1, 1992. As discussed above under part A of "Arguments," the claimed subject matter is fully supported by the priority application. Accordingly, the Pancholi reference is not available as prior art and this rejection should be reversed by the Board.

Further, even if Pancholi were available as a reference, it would not anticipate the cells of the present claims. All of the claims specify dendritic cells derived from an *in vitro* culture of dendritic cell precursors. As described in the specification, the cells of the invention are cultured in GM-CSF, which was surprisingly found to promote the proliferation *in vitro* of precursor dendritic cells; these precursors can be used to provide large populations of antigen-activated

dendritic cells. Pancholi merely teaches the isolation of dendritic cells directly from blood. Thus, the process used to make the claimed cells is different from the process described by Pancholi, and the cells that result from each process are also different in at least two significant ways. First, the present invention provides dendritic cells derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells, thereby overcoming the previously existing problem in the art of not being able to obtain sufficient quantities of dendritic cells for clinical treatment (as discussed in the present specification, *e.g.*, on page 2, lines 21-26 and page 8, lines 3-11). Second, dendritic cells prepared according to the claimed methods are more effective at presenting antigen to T cells *in vitro* than the cells reported by Pancholi. Particularly, results obtained with dendritic cells prepared according to the claimed methods show significant stimulation of T cells at a dendritic cell to T cell ("DC:T") ratio of 1:1000. This is shown, for example, in Figure 15A, which presents the results of an experiment in which T cells respond to stimulation by immature or mature BCG-pulsed dendritic cells prepared according to the methods of the invention at DC:T cell ratios of 1:100 and 1:1000. In contrast, Pancholi's DCs show no stimulation of T cell response at a much lower DC:T ratio of 1:100 (see Figure 2b). Thus, the cells of the present invention are more effective at presenting antigen to T cells *in vitro* than the cells taught by Pancholi and are therefore different from the cells taught by Pancholi. Because the cells taught by Pancholi are different from the claimed cells, the Pancholi reference would not anticipate the claims even if it were available as prior art, which it is not. Accordingly, this rejection should be reversed by the Board.

35 U.S.C. §103—Obviousness

"[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art." *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to

support the legal conclusion of obviousness." *Id.* at 417-418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the invention as a whole would have been obvious. See, *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782 (Fed. Cir. 1983). When assessing the patentability of product-by-process claims over the prior art, the structure implied by the process steps should be considered, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979).

C. The final Office Action alleges that claims 99, 101, 104-113, 116, 120, and 142-145 are obvious under 35 U.S.C. § 103(a) over Inaba *et al.* ((1990) *J. Exp. Med.* 172: 631-640) in view of Steinman *et al.* ((1988) *Ann. N.Y. Acad. Sci.* 546: 80-90) and Markowicz and Engleman ((1990) *J. Clin. Invest.* 85: 955-961).

The Office Action concludes (page 5, last paragraph of block quote) that

> "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add GM-CSF to a cell culture of DCs [(dendritic cells)]such as the mouse cultures of Inaba et al. and Steinman et al. or the human cultures of Steinman et al. and Markowicz and Engleman. The ordinarily skilled artisan would have added GM-CSF to DC cultures given the teachings of Steinman et al., that, DC 'maturation is driven by factors such as IL-1 and GM-CSF,' etc. and Markowicz and Engleman, that, 'GM-CSF ... profoundly affects the morphology and viability of DCs isolated from peripheral blood....' Accordingly, the GM-CSF-cultured DCs as claimed are obvious in view of the combined prior art."

Appellants respectfully disagree with this rejection because none of the references, nor any combination thereof, teaches the claimed compositions or the method steps specified in the claims that are necessary to produce them. The Inaba reference includes experiments on dendritic cells but does not teach anything about GM-CSF and also does not teach or suggest that dendritic cell precursors even exist. None of the references, either alone or in any combination, teach or suggest that the use of GM-CSF to culture dendritic cell precursors *in vitro* produces an

enriched and expanded population of proliferating dendritic cell precursors that can be used to produce a large population of mature dendritic cells expressing modified antigen.

The Office Action cites the Markowicz and Engleman reference as teaching that "'GM-CSF ... profoundly affects the **morphology and viability** of DCs isolated from peripheral blood...'" and concludes that one of skill would have been motivated to add GM-CSF to DC cultures. However, rather than suggesting such a combination, the Markowicz and Engleman reference instead teaches away from the claimed invention and particularly teaches away from the use of GM-CSF to induce proliferation. Particularly, Markowicz and Engleman conclude that in the presence of GM-CSF, "the number of viable cells as well as the number of branched cells per well **remained stable over time, suggesting that GM-CSF does not cause DC to divide and proliferate**" (sentence bridging page 958-959; emphasis added). This is supported by Markowicz and Engleman's Figure 4 (on page 959), which shows that there was no significant increase in the number of viable cells (as well as differentiated DC) "throughout the culture period" (see Figure 4 legend on page 959). In view of this teaching away by Markowicz and Engleman, one of skill in the art would not have added GM-CSF to induce cell proliferation of Inaba's cell cultures and so would not have been motivated to produce the claimed invention.

The third reference cited in this rejection of claims is Steinman *et al.* ((1988) *Ann. N.Y. Acad. Sci.* 546: 80-90), which is cited in the Office Action as teaching:

> "the enrichment and culturing of both mouse and human immature DCs found in blood, as well as bone marrow (see pages 81-83) and that, 'maturation is driven by factors such as IL-1 and GM-CSF' (see page 83). The reference further teaches that 'GM-CSF is critical in mobilizing active DCs at the onset of a cell-mediated immune response' (see page 88)."

Appellants disagree and respectfully submit that the Steinman reference teaches away from the claimed invention because it states that GM-CSF has a role *in vivo* in **maturation** of cells in certain tissues and proposes that GM-CSF may be involved in **mobilizing** DCs at the onset of a cell-mediated immune response. The Steinman reference does not teach or suggest that culture of dendritic cell precursors in GM-CSF can produce a population of proliferating dendritic cell precursors as taught by Applicants, or the mature dendritic cells resulting from such a process, as presently claimed.

The Steinman reference also discusses "immature forms of dendritic cells," but states that (paragraph bridging pages 83 and 84):

> "The term 'immature' is used, because these populations must be cultured for 1-2 days before optimal levels of surface Ia and accessory function are expressed."

That is, the Steinman reference teaches that "immature" DCs need only be cultured for 1-2 days, and that this time is necessary for maturation. Thus, while discussing "immature" DCs and, separately, a role for GM-CSF in certain DC functions, the Steinman reference does not teach or suggest that GM-CSF plays any role in stimulating cell proliferation of DCs, particularly of dendritic cell precursors, and thus does not teach or suggest the claimed invention.

When assessing the patentability of product-by-process claims over the prior art, the structure implied by the process steps should be considered, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979). Here, the claims are drawn to an *in vitro* composition of cells derived from an *in vitro* culture of an enriched and expanded population of proliferating precursors by a method comprising culture in GM-CSF, which surprisingly was found to promote that proliferation; further, these cells are cultured *in vitro* in the presence of antigen and express modified antigen.

The claimed cells differ from previously reported cells, for example, in their ability to take up antigen even after extended periods of culture. Specifically, for example, the fresh spleen cells taught by the cited Inaba reference differ in at least several significant ways from the *in vitro* compositions of the present invention. First, as taught by the Inaba reference ("Inaba"), fresh spleen cells can only take up antigens for a short time, and lose this ability in culture. The Inaba reference states:

> "As will be evident in Results, it was necessary to expose fresh rather than cultured dendritic cells to a foreign protein to successfully charge these APC with antigen."

(see Inaba *et al.* (1990), *e.g.*, at page 632, left column, first full paragraph)

Further, Inaba *et al.* state:

> "We conclude that freshly isolated dendritic cells can be successfully pulsed with a variety of soluble protein antigens *in vitro*, but that it is important to administer the antigen shortly after isolating the dendritic cells from the spleen."

(see Inaba *et al.* (1990) at page 632, right column, first paragraph of "Results" section).

In contrast to the cells taught by Inaba, the cells of the present invention can take up antigen after being cultured for many days (see, *e.g.*, Figure 13, showing uptake and expression of antigen after cells had been cultured for 6 days in GM-CSF). Because fresh spleen cells like those of Inaba's lose their ability to take up antigen in culture, they cannot give rise to enriched and expanded cell populations which take up and then express modified antigen to which they have been exposed *in vitro*, as required by the present claims. The cells of the present invention provide enriched and expanded cell populations in clinically useful quantities, a benefit resulting from Appellants' innovative step of culturing the cells in GM-CSF so as to obtain proliferating dendritic cell precursors. Thus, the claimed compositions provide a number of advantages that result from the novel methods of their production, which are not taught or suggested by the prior art.

As further evidence of nonobviousness, Appellants note that the Examiner previously withdrew an obviousness rejection over the cited Inaba reference for the stated reason that "an objective and quantifiable difference between the DCs of the prior art and the DCs of the instant claims was established (the inability of the DCs of Inaba et al. to capture antigen after several days of culture)" (see the Final Office Action of November 18, 2008, page 5). This obviousness rejection was later withdrawn (in the Office Action of 13 August 2004) because Appellants' "arguments that the cells of the instant invention are not the cells of the reference because the cells of the reference were not cultured in GM-CSF, has been found convincing." Now, however, the present obviousness rejection similarly cites references (including the same Inaba reference) that do not teach or suggest the use of GM-CSF to culture dendritic cell precursors *in vitro* to produce an enriched and expanded population of proliferating dendritic cell precursors, nor that these cells can be used to produce a large population of mature dendritic cells expressing modified antigen. In view of this as well as the discussion above, Appellants respectfully submit that the Examiner has not made out a *prima facie* case of obviousness.

In summary, culture of the dendritic cell precursors in GM-CSF, as discovered by Appellants, is essential to the development of *in vitro* cultures of proliferating precursor cells and provides a number of advantageous properties to the resulting dendritic cells, including embodiments where the cells have been cultured *in vitro* in the presence of an antigen and give rise to mature dendritic cells expressing modified antigen as required by the claims. None of the cited references teaches or suggests this critical feature of the methods that produce the claimed

cells. Accordingly, the claimed invention is not rendered obvious by any of the cited references or any combination thereof and this rejection should be reversed by the Board.

35 U.S.C. §112, first paragraph—Written Description

The disclosure as originally filed need not provide "*in haec verba* support for the claimed subject matter at issue," rather, the disclosure should convey to one skilled in the art that the inventor had possession of the invention at the time of filing. *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). The Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

D. Under 35 U.S.C. § 112, first paragraph, was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly containing new matter?

The final Office Action states that the specification and claims as originally filed provide support for a method step of allowing culture for a time sufficient to allow the antigen to bind to the dendritic cells "but not for the additional limitation of sufficient time to process and express the antigen."

Support in the present specification for each claim is discussed in the Summary of Claimed Subject Matter (section V) above and is also described in detail for the '612 priority application in the chart included as Appendix A. Specific support for the last step of claim 101 and 145 and the corresponding step of claim 120 are as follows:

> "Dendritic cells bind and modify antigens in a manner such that the modified antigen when presented on the surface of the dendritic cell can activate T-cells to participate in the eventual production of antibodies. The modification of antigens by dendritic cells may, for example, include fragmenting a protein to produce peptides which have regions which specifically are capable of activating T-cells." (page 5, lines 20-27)

> "The antigen-activated dendritic cells of the invention are produced by exposing antigen, *in vitro*, to the dendritic cells prepared according to the method of the invention. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells." (page 34, line 34 through page 35, line 3)

> "Cells should be exposed to antigen for sufficient time to allow antigens to be internalized and presented on the cell surface." (page 36, line 31-33)

> "Foreign and autoantigens are processed by the dendritic cells of the invention to retain their immunogenic form. The immunogenic form implies processing the antigen through fragmentation to produce a form of the antigen that can be recognized by and stimulate T cells." (page 34, lines 16-20)

Thus, the specification provides support for the relevant step of claim 101 (specifically, "culturing the dendritic cells *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to bind to the dendritic cells, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells"), claim 120 (specifically, "exposing the cells to antigen *in vitro*, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells), and 145 (specifically, "pulsing the dendritic cells with an antigen, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells"; the term "pulsing" is synonymous with exposing the cell to a protein antigen, for example, as it is used in the Abstract of the Disclosure). While each independent claim (101, 120, and 145) includes slightly different terminology, the specification provides support for the terminology of each claim. Accordingly, the Board should reverse this rejection.

35 U.S.C. §112, second paragraph—Indefiniteness

35 U.S.C. §112, second paragraph is satisfied if "one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims meet the requirements of 35 U.S.C. §112, second paragraph, if "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

E. Under 35 U.S.C. §112, second paragraph, was it proper to reject claim 120 as allegedly indefinite?

The final Office Action alleges that claim 120 is indefinite because "it is unclear whether or not the actions of the claim are actually intended to be method steps. If so, then the steps must be separated and indented as is required of all method steps."

Claim 120 is as follows:

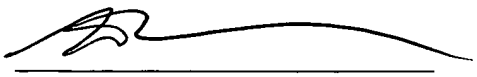
> "An *in vitro* composition comprising mature dendritic cells expressing a modified antigen and derived from an *in vitro* culture of a population of proliferating dendritic cell precursor cells **by a method comprising culturing** dendritic cell precursor cells in a culture medium comprising GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors**; serially subculturing** the proliferating dendritic cell precursors at intervals which provide for the continued proliferation of said dendritic cell precursors**; and exposing** the cells to antigen *in vitro*, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells." (bold font added)

As shown by the terms placed in bold font, the claim recites that the dendritic cells are derived from a population of proliferating precursor cells "**by a method**" and then recites three clauses, each of which includes an active verb. The clauses are separated by semicolons. In view of the explicit statement in the claim regarding the use of a method and the proper use of active verbs and punctuation, Applicants' representative believes the claim meets the requirements for clarity under 35 U.S.C. § 112, second paragraph. Further, the grounds for the rejection—that the lack of indentation of the method steps renders the claim indefinite—does not appear to have any basis in the statute itself. Therefore, this rejection should be reversed by the Board.

CONCLUSION

For the reasons discussed above, the Examiner's rejections are improper and should be reversed by the Board. Appellants submit that the pending claims are in condition for allowance and earnestly solicit an early notice to that effect.

Respectfully submitted,



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VIII. CLAIMS APPENDIX

99. The pharmaceutical composition according to claim 116, wherein the dendritic cells express an amount of the modified antigen to provide between about 1 to 100 micrograms of the modified antigen in said pharmaceutical composition.

101. An *in vitro* composition comprising mature dendritic cells expressing modified antigen and derived from an *in vitro* culture of an enriched and expanded population of proliferating dendritic cell precursors by a method comprising:

providing a tissue source comprising dendritic cell precursors;

treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors;

treating the tissue source to obtain a population of cells suitable for culture *in vitro*;

culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain nonadherent cells and cell clusters;

subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors;

serially subculturing the cell aggregates one or more times to enrich the proportion of dendritic cell precursors; and

continuing to culture the dendritic cell precursors for a period of time to allow them to mature into mature dendritic cells;

culturing the dendritic cells *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to bind to the dendritic cells, wherein the dendritic

cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.

104. The composition according to claim 101, wherein the tissue source is blood.

105. The composition according to claim 101, wherein the tissue source is bone marrow.

106. The composition according to claim 101, wherein GM-CSF is present in the culture medium at a concentration of about 1-1000 U/ml.

107. The composition according to claim 104, wherein the concentration of GM-CSF in the culture medium is about 30-100 U/ml.

108. The composition according to claim 105, wherein the concentration of GM-CSF in the culture medium is about 500-1000 U/ml.

109. The composition according to claim 101, wherein the cell aggregates are blood derived and are subcultured from about one to five times.

110. The composition according to claim 101, wherein the cell aggregates are subcultured one to five times.

111. The composition according to claim 101, wherein the culture medium is selected from the group consisting of RPMI 1640, DMEM and α-MEM, and wherein the culture medium is supplemented with serum.

112. The composition according to claim 104, wherein the tissue source is treated to remove red blood cells.

113. The composition according to claim 105, wherein the tissue source is treated to remove B cells and granulocytes.

116. A pharmaceutical composition comprising a therapeutically effective amount of the composition according to claim 101.

120. An *in vitro* composition comprising mature dendritic cells expressing a modified antigen and derived from an *in vitro* culture of a population of proliferating dendritic cell precursor cells by a method comprising culturing dendritic cell precursor cells in a culture medium comprising GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors; serially subculturing the proliferating dendritic cell precursors at intervals which provide for the continued proliferation of said dendritic cell precursors; and exposing the cells to antigen *in vitro*, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.

142. The composition according to claim 101, wherein the dendritic cell precursors are human.

143. The composition according to claim 142, wherein the dendritic cell precursors are obtained from blood.

144. The composition according to claim 142, wherein the dendritic cell precursors are obtained from bone marrow.

145. An *in vitro* composition comprising antigen-activated dendritic cells expressing modified antigens and derived from an *in vitro* culture of proliferating dendritic cell precursors by a method comprising:

a) providing a tissue source comprising dendritic cell precursors;

b) treating the tissue source to obtain a population of cells suitable for culture *in vitro*;

c) culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain nonadherent cells and cell clusters;

d) subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors;

e) serially subculturing the cell aggregates one or more time to enrich the proportion of dendritic cell precursors;

f) continuing to culture the dendritic cell precursors for a period of time sufficient to allow them to mature into mature dendritic cells; and

g) pulsing the dendritic cells with an antigen, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.

IX. EVIDENCE APPENDIX

1. Pancholi *et al.*, "Dendritic cells efficiently immunoselect mycobacterial-reactive T cells in human blood, including clonable antigen-reactive precursors," *Immunology* vol. 76, pp. 217-224 (1992).

This reference was previously made of record by the Examiner and is discussed on page 4 of the final Office Action. A copy is attached.

2. Inaba *et al.*, "Dendritic cells pulsed with protein antigens *in vitro* can prime antigen-specific, MHC-restricted T cells *in situ*," *J. Exp. Med.* vol. 172, pp. 631-640 (1990).

3. Steinman *et al.*, "The sensitization phase of T-cell-mediated immunity," *Ann. N.Y. Acad. Sci.* vol. 546, pp. 80-90 (1988).

4. Markowicz and Engleman, "Granulocyte-macrophage colony-stimulating factor promotes differentiation and survival of human peripheral blood dendritic cells *in vitro*," *J. Clin. Invest.* vol. 85, pp. 955-961 (1990).

References "2," "3," and "4" are discussed on page 5 of the final Office Action. References "2" and "4" were cited in an IDS in 2001, and references "3" and "4" were made of record by the Examiner in 2009. Copies are attached.